Diagnosis and Treatment of Diabetic Patients Requiring Insulin Who Repeatedly Manifest Hyperglycemia and Hypoglycemia Due to Anti-Insulin Antibodies

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Although anti-insulin antibodies (IAs) are often observed in patients treated with general regimens of insulin, their existence is not thought to be related to hypoglycemia.[1] However, IA-positive patients treated with human insulin may manifest unexplainable hypoglycemia.[2–5] The IAs of these patients have a lower affinity and a higher binding capacity than those from patients with insulin autoimmune syndrome (IAS)[6] or those who do not develop hypoglycemia when treated with insulin. Ceasing insulin administration[2] and switching to insulin analogs,[3] steroid therapy,[4] or double filtration plasmapheresis (DFPP)[5] are all therapies that have been advocated to treat such patients.

Recently, we described analog insulin-receiving patients who developed severe daytime hyperglycemia and morning hypoglycemia associated with IA formation.[7] Such cases seem to be augmenting with the spread of insulin analog treatment, and, unfortunately, they did not appear to respond well to the aforementioned therapies. Thus, we set out to define the clinical characteristics of these patients who generated IAs and manifested unexplainable fluctuations in blood glucose levels while receiving insulin analogs and to determine how best to treat them.

Methods

The characteristics of six insulin-treated patients with IAs who repeatedly manifested unexplainable hyperglycemia and hypoglycemia (Group D) were investigated. They were compared with the same features in six patients seen to have IAs when a cohort of 100 insulin-treated patients without unexplainable hyperglycemia or hypoglycemia were screened randomly (Group B), three patients with IAS (Group A), and three insulin-treated patients with IAs who did not manifest hyperglycemia but occasionally developed inexplicable hypoglycemia (Group C). The binding capacity and affinity of the IAs were compared between the groups using Scatchard plots. Plasma immunoreactive insulin (IRI) and plasma free insulin were measured at the time of hyperglycemia or hypoglycemia. In addition, the clinical course of each of the six patients in Group D was analyzed after treatment. This study was conducted after obtaining informed written consent from all subjects.

Results

When the characteristics of IA-positive patients were examined (Table 1), the Group D patients were older on average than those in the other groups, and all of the patients were male. Except for the Group A patients, all the other patients received insulin analog treatment, yet only the patients in Group D manifested marked daytime hyperglycemia. This hyperglycemia was not affected by changes in the insulin preparation,[3] increased doses, or intravascular administration. By contrast, inexplicable morning hypoglycemia was observed in Groups A, C, and D. Although the hypoglycemia in Group A was moderate, it was severe in Groups C and D. Moreover, whereas hypoglycemia occurred on several days each month in Group C, it was experienced almost every morning in Group D.

The IAs from patients in Group D had higher IA-binding rates (IABRs) than those in the other groups, yet the IRI levels in Group D were higher than those of the other groups. Whereas IA affinity was highest in Group B, it decreased in Groups A and C before reaching the lowest values in Group D. Indeed, the affinity of the IAs in Group C and D was about three orders of magnitude lower than in Group B. Conversely, the binding capacity was lowest in Group B, increasing in Groups C and A before reaching the highest values in Group D. Significantly, the binding capacity of the IAs from Group D patients was ~100–1,000 times greater than that of the IAs from Group B patients (Table 1). The binding capacity of insulin antibodies was considered to be a possible cause of daytime hyperglycemia, whereas the affinity of insulin antibodies seemed to be more closely related to morning hypoglycemia.

Although the IAs from Group C patients had low affinity on average, their binding capacity was

Table 1. Clinical Features of Each Group of Patients With Anti-Insulin Antibodies

Group	A	B	C	D
n	3	6	3	6
Sex (male/female)	1/2	2/4	1/2	6/0
Age (years)*	53.3 ± 9.0	59.3 ± 13.4	64.0 ± 7.1	82.3 ± 5.7
A1C (%)*	5.4 ± 0.3	6.4 ± 0.3	5.6 ± 0.5	8.1 ± 1.0
Insulin treatment	—	+	+	+
Daytime hyperglycemia	—	—	—	++
Morning hypoglycemia	+	—	+	++
Immunoreactive insulin (μU/ml)*	519.5 ± 244.7	202.7 ± 171.2	126.4 ± 19.3	2135.5 ± 924.9
C-peptide (ng/ml)*	8.0 ± 0.8	1.4 ± 0.6	0.8 ± 0.3	0.6 ± 0.2
Insulin antibody binding rate (%)*	47.5 ± 11.1	30.8 ± 6.1	20.1 ± 3.3	85.8 ± 5.8
Capacity 10^{-8} (M)**	17.8 (12.4–46.3)	0.4 (0.1–1.1)	6.7	185.5
			(6.3–8.4)	(44.6–336.0)
Affinity 10^{8} (M^{-1})**	0.22 (0.011–0.31)	3.77 (0.04–7.21)	0.004 (0.003–0.005)	0.003 (0.0004–0.008)
Treatment	Observation	Observation	Observation	Immunosuppressive therapy

**Mean ± SD.*
***Median (range).*

below that of the IAs from Group D. These data imply that the IAs from Group C patients can release only a small amount of insulin, which may explain the lower frequency of hyperglycemia or hypoglycemia in Group C patients than in Group D patients. There was one patient in Group B whose IAs had a low affinity (0.04×108 M^{-1}), although their binding capacity was also low (0.62×10^{-8} M), which might explain why she did not develop hypoglycemia or hyperglycemia.

Whereas the total IRI levels of patients in Group D were very high (> 1,000 μU/ml), the C-peptide plasma levels were very low (< 1 ng/ml). Hence, most of the plasma insulin would appear to be exogenous, with little endogenous insulin. The endogenous insulin secreted by Group D patients was too weak to cease exogenous insulin administration. Indeed, although ceasing insulin administration decreased the total IRI and resolved the hypoglycemia, severe hyperglycemia developed.

Although free plasma insulin levels were very low (< 5 μU/ml), high IRI levels were observed during hyperglycemia, suggesting the presence of IAs binding to numerous insulin molecules. Alternatively, very high free plasma insulin levels (> 1,000 μU/ml) and high plasma IRI levels were observed during hypoglycemia, suggesting that the IAs released insulin abundantly.

All patients in Group A and one patient in Group D had IA-sensitive human leukocyte antigen (HLA) DRB1*0406, whereas the other five patients in Group D had HLA DRB1*0405, which may protect against IA development.

In Group D, DFPP removed the IAs,[5] but this therapeutic effect only persisted for a short period. Although prednisolone therapy was effective,[4,5] its many side effects precluded its long-term use. Accordingly, cyclophosphamide pulse therapy (CPT) was combined with steroid therapy, decreasing the prednisolone dose gradually over several months. This CPT (300 mg/month, 10 cycles) in combination with gradually decreasing predniso-

lone administration reduced A1C from 8.1 ± 1.0 to 6.3 ± 0.2%, and the requirement for insulin from 104.5 ± 45.8 to 24.8 ± 3.8 units/day. The severe morning hypoglycemia disappeared, and the IABRs diminished from 85.8 ± 5.8 to 16.1 ± 10.6%. Scatchard plots showed that the reduction in the binding capacity and the increase in the affinity of IAs paralleled the reduction in IABRs.

Conclusions

CPT combined with prednisolone therapy seems to be the most effective treatment to control the hyperglycemia and hypoglycemia associated with the presence of IAs in diabetic patients treated with insulin. However, because such patients are elderly, which may be a hallmark of this disease, the patients' social indications should also be considered to provide treatment accordingly, as well as remaining vigilant to prevent infections and adverse reactions to the immunosuppressant. Some physicians jump to the conclusion that their patients' blood glucose fluctuations are caused by a lapse in their dietary regimen, inappropriate exercise, or badly timed insulin injections. Thus, they often fail to investigate whether more suitable treatment is needed.

Five patients in Group D were receiving (or had received) injections of biphasic insulin aspart (BIAsp)-30. Three patients in Group D developed symptoms after switching to the insulin analog, whereas they developed no such symptoms while undergoing long-term treatment with human insulin. Insulin analogs, especially BIAsp-30, may be more likely to induce the appearance of pathological IAs. Thus, it will be necessary to determine whether this is the case in a larger number of IA-positive patients.

There are many cases of elderly patients who are given insulin analogs (especially BIAsp-30) without due care. This report aims to serve as a warning to prevent these errors.

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